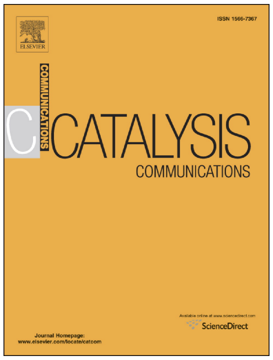

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Cross-linked polystyrene-TiCl$_4$ complex as a reusable Lewis acid catalyst for solvent-free Knoevenagel condensations of 1,3-dicarbonyl compounds with aldehydes

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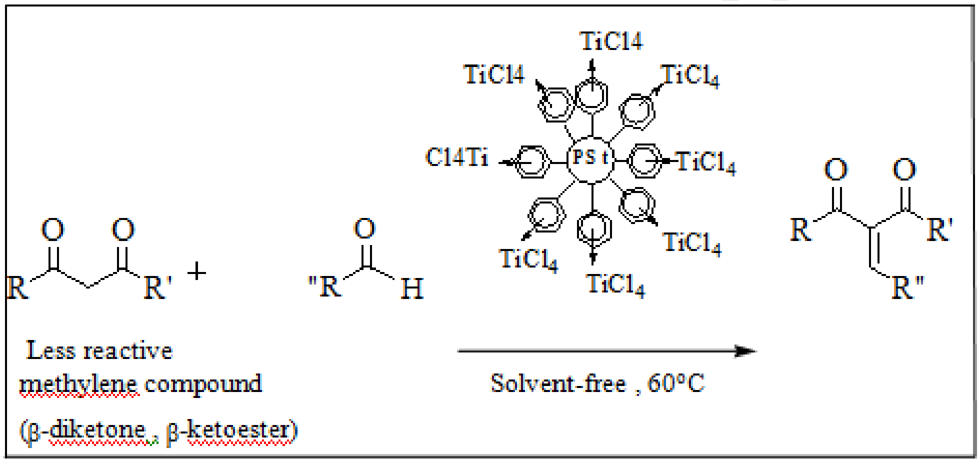
Graphical abstract



Abstract

Cross-linked polystyrene copolymer beads with the average particle size in the range of (50-80 mesh size) were prepared by a new method, characterized and functionalized with titanium tetrachloride to afford the corresponding polystyrene-titanium tetrachloride complex in one step reaction and characterized by FT-IR, UV, TGA, DSC, XRD, SEM, BET. This polymer metal complex (PS/TiCl$_4$) was used as a heterogeneous, recoverable, reusable Lewis acid for solvent-free Knoevenagel condensations of 1,3-diketones with aromatic aldehydes under green and mild conditions. The rate of reactions was found to decrease with an increasing percentage of crosslinking and the mesh size of the copolymer beads. This complex showed good stability and catalytic activity in the Knoevenagel reactions.

Keywords: Cross-linked polystyrene copolymer bead ; Polymeric catalyst; Heterogeneous catalyst; Solvent-free condition; Knoevenagel condensation

1. Introduction

Knoevenagel condensation is a synthetically important reaction both in chemistry and in material science wherein the end products are generally the trisubstituted alkenes. This reaction is widely used in the synthesis of natural products, biologically important molecules, functional polymers, and photonic materials [1,2]. It may be carried out either in homogeneous or heterogeneous phase. Many homogeneous base and Lewis acid catalysts have been employed to accomplish this reaction [3-9]. However, using these catalysts have numerous disadvantages such as waste production, significant problems in handling, disposal and regeneration due to their toxic and corrosive nature, and no catalyst recovery. For overcoming these drawbacks one approach is replacing of conventional, toxic, and polluting homogeneous catalysts with eco-friendly reusable heterogeneous catalysts to combine the advantages of these catalysts with those of heterogeneous support materials including higher atom efficiency, stability, operational simplicity, selectivity and recyclability. The development of polymer-immobilized catalysts is a rapidly growing field, which has great importance in conventional and combinatorial organic synthesis mainly because of the easy separation and reusability of polymer-supported catalysts. The polymeric catalysts also present one of the most powerful tools for”green”sustainable chemistry, in the sense that they can be easily recovered and reused many times.

Many heterogeneous catalysts, such as Ni-SiO_2-supported catalysts [10], nitrogen-doped carbon materials [11], MCM-41 [12], zeolites [13], enzymes [14], amino groups immobilized on silica gel [15], Lewis acidic/basic bifunctional organobismuth complex in ionic liquids [16], and other catalysts based on alumina [17], silica sulfuric acid [18,19], zinc and magnesium oxides [20], microporous polyurethane [21], zeolite membrane microreactor [22-24] have been exploited as catalysts for the Knoevenagel condensation.

There has been a long standing desire in preparative chemistry to avoid waste, to substitute benign chemicals and solvents for toxic ones and to use solvent-less reactions. Most of the Knoevenagel condensations in literature are reactions of highly reactive methylene active compounds carrying two electron withdrawing groups such as malononitrile and ethyl cyanoacetate with aldehydes [25]. However, only few examples of 1,3-diketones as starting materials in the green known condensations are reported [26]. Very likely, such compounds are less reactive than the other ones since their attitude to form a stable six-membered enolate which makes it less reactive [6,7], hence a green procedure for

Knoevenagel condensations between aldehydes and 1,3-dicarbonyl compounds using highly efficient and reusable heterogeneous catalysts either solvent-free or in water is always desirable.

Titanium tetrachloride as a powerful Lewis acid has found many applications in industry. However, this compund is a liquid and highly aggressive material that creates clouds of HCl when is exposed to air and moisture. Therefore, its handling needs serious precautions. Our attempt is to immobilize $TiCl_4$ directly into the polymer matrix for reaching the high loading catalyst in one step reaction without functionalization of the polymer matrix. In continuation of our previous experience on the synthesis of cross-linked polymer beads as supports using conventional synthetic suspension stabilizers and the recent works on the use of polymeric catalysts in organic transformations [27-29], herein we report the preparation of cross-linked polystyrene copolymer beads with the given particle size and morphology using guar gum from bioresource as new alternative synthetic suspension stabilizers by carrying out cross-linking suspension copolymerization and immobilizing of $TiCl_4$ on them in one step without functionalization of the copolymer bead matrix, and then investigation of catalytic activity of the resulting polystyrene-$TiCl_4$ complex as a stable, highly active and reusable heterogeneous catalyst in the Knoevenagel condensations of 1,3-dicarbonyl compounds with various aromatic aldehydes in a solvent-free media and mild conditions in absence of any water absorbing drying agents (Scheme 1). The procedure was environmentally friendly and efficient, and the water stable PS/$TiCl_4$ catalyst possessed high catalytic activity and could be easily separated, recycled and reused several times without significant loss of activity. This PS support with lower crosslinking degree and mesh size prepared using conventional suspension stabilizer through suspension polymerization has been recently used for the synthesis of PS/$TiCl_4$ [30].

<Scheme 1>

2. Experimental

2. 1. Preparation of cross-linked polystyrene copolymer beads

In a 250 ml three-necked round-bottomed flask equipped with a mechanical stirrer, nitrogen gas inlet, and reflux condenser that is placed in a thermostated water bath, a mixture of distilled water (500 parts) containing guar gum (GG, 2 wt% in relation to the monomers) and NaCl (1% w/v in relation to water volume) was first introduced and stirred at room temperature for 30 min. While stirring, nitrogen was purged from the mixture, the suspending medium was then heated to the reaction temperature. A mixture of the monomers (St and several weight ratios of DVB cross-linker, 4, 6, 8, 10%) were first mixed well with the porogen (toluene-heptane (3:2) mixture) to form an organic phase in which, the initiator, AIBN, was added in the amount of 1 mol% of monomers. The organic phase mixture was then added dropwise to the aqueous phase, through a dropping funnel to the flask for about 30 min (The volume ratio between the two phases (organic/aqueous) was kept constant at 1/5). The stirring rate was kept at 350-400 rpm and the polymerization was allowed to proceed at 80 ^{o}C for 18 h. After the polymerization, the copolymer beads were filtered out on a Buchner funnel under vacuum, and treated in 1N HCl at boiling temperature for 15 min, washed twice with hot water, and then vacuum filtered to remove the stabilizer. The copolymer beads were extracted thoroughly with acetone for a few hours in a soxhlet apparatus to remove porogen and residual monomers, and then were washed twice with acetone, two times with methanol to ensure complete removal of impurities. Finally, the samples were dried in a vacuum oven at 50 ^{o}C for at least 10 h. The overall conversion of the monomers to solid copolymer was determined gravimetrically. Of these beads the 50-80 mesh size (or 170-290 μm) beads were used in the subsequent studies.

2. 2. Preparation of polystyrene-supported titanium tetrachloride (PS/TiCl$_4$)

The above prepared polymer beads (8% DVB, grain size range: (170-290 μm, 50-80 mesh size) suspended in 6 ml of dry carbon disulfide in a round bottomed flask equipped with an overhead stirrer and left to swell for 0.5 h at room temperature. A solution of anhydrous TiCl$_4$ (2 g) in dry carbon disulfide (4 ml) was added to the dispersed polystyrene bead solution under strring. The mixture was kept under refluxing conditions and stirring for 1 h under a nitrogen atmosphere. The reaction mixture was allowed to cool at room temperature and cold water (50 mL) was then cautiously added to hydrolyze the uncomplexed TiCl$_4$. The mixture was stirred until the bright red color disappeared, and the polymer became light yellow. The polymer beads were collected by filtration through suction and washed thoroughly with water (100 mL) and then with ether (10 mL) and chloroform (10 mL), respectively. The light yellow colored catalyst sample was further dried in a vacuum oven overnight at 50 ^{o}C before use. The chlorine content of PS/TiCl$_4$ was 11.62 % analyzed by the Mohr titration method [27-31] and the loading capacity of TiCl$_4$ on the polymeric catalyst or the amount of TiCl$_4$ complexed with polystyrene was calculated to be 0.824 mmol/g complex bead.

2. 3. Determination of the quantity of TiCl$_4$ complexed

The PS-$TiCl_4$ complex samples were decomposed by burning via the sodium fusion method. The amount of $TiCl_4$ complexed with polystyrene was calculated from the chlorine content. It was also determined by the atomic absorptiom spectrophotometry technique from the titanium content.

2. 4. Determination of acidity (pH) of the PS-$TiCl_4$ complex

The catalyst sample was hydrolyzed in a acetone-water solution (60%, 3/2 v/v) at room temperature. The pH of the resultant solution was determined by using a standard pH meter.

2. 5. Typical procedure for the solvent-free Knoevenagel reaction

A mixture of aromatic aldehyde (1 mmol), acetylacetone (6 mmol) was charged into a 25 ml of round-bottomed flask equipped with a magnetic stirrer, followed by adding PS/$TiCl_4$ containing certain amount of $TiCl_4$ (0.12 gr, 0.1 mmol of $TiCl_4$). The resulting mixture was heated at 60 ^{o}C in a water bath with stirring for an appropriate period of time under solvent-free conditions (Table 1). The progress of the reaction was indicated by TLC (silica gel, petroleum ether or hexane/ethyl acetate). After completion of the reaction, the reaction mixture was allowed to cool to room temperature, and the catalyst was filtered and washed with ethyl acetate several times. The recovered catalyst was dried at 60 ^{o}C for 2 h. The washings were collected and combined with the filtrate. The organic solution was concentrated/evaporated under reduced pressure in a rotary evaporator, or treated by chromatography on a silica gel column (eluted by a mixture of petroleum ether and ethyl acetate), leading to the substituted olefin product with satisfactory purity.The structure of which was confirmed by m.p. data and with ^{1}H NMR, and IR techniques. Characterization of the products was performed by comparison of their FT-IR, ^{1}H NMR, and physical data with those of the authentic samples. Conversion was defined as a percentage of the starting aldehyde converted into products. The products were characterized by comparison of their physical data with those of the known samples or by comparison of their IR and NMR. The same procedure was applied for the condensation of β-ketoesters and dimethyl malonate with aromatic aldehydes (Table 3, entries 10-26). The characteristic data of selected compounds **3dk**, **3dj** are provided in supplementary data.

3. Results and discussion

3.1. Synthesis and characterization of crosslinked poly (St-DVB) beads and titanium tetrachloride complex with them

The polymeric carrier beads as polymer support were synthesized by carrying out aqueous cross-linking suspension radical copolymerization of St-DVB monomers. For lightly cross-linked resins, swelling in common organic solvents is an important factor in the success of solid-phase reactions. A polymer with high degree of cross-linking has a network consisting of dense and relatively larger number of inaccessible domains leading to less functionalization. For this reason, in the present study, the copolymer beads containing (8 wt.%) of DVB as cross-linker were utilized as the polymer carrier. All resins were sieved to a range of 25-80 mesh. The 50-80 mesh beads were used as carrier in the polymer supported catalysts.

The PS/$TiCl_4$ complex was prepared by complexation of cross-linked PS with $TiCl_4$ in one step reaction without functionalization of the polymer matrix. The copolymer beads (DVB, 6-8%) were combined with $TiCl_4$ in carbon disufide or carbon tetrachloride to form a stable complex. The DVB-crosslinked PS-TiCl4 complex was prepared by the concise route outlined in Scheme S1 (see supplementary data). To confirm the immobilization of $TiCl_4$ on polymer carrier, FT IR spectroscopic studies were firstly carried out with PS/$TiCl_4$ and PS. Figs. S2 are the IR spectra of PS and PS/$TiCl_4$, respectively (see supplementary data). Comparing the FT IR spectra of PS and PS/$TiCl_4$ catalyst, peak intensity centered at 3025 cm^{-1} significantly decreases, indicating a reduction in the electron density on the carbon-carbon (π) double conjugated bond. This is due to the donation of electron density from π bond to the vacant d orbital of Ti in $TiCl_4$. Further, the obvious difference between the FTIR spectra of polystyrene-titanium tetrachloride complex and crosslinked polystrene was at 1500-1600 cm^{-1} and at 500-800 cm^{-1}. The FTIR spectrum of PS/$TiCl_4$ showed new peaks at 1500-1590 cm^{-1} due to for C-C stretching, 500-800 cm^{-1} for benzene ring C-H bending, indicating the donor-acceptor interaction of carbon-carbon (π) bond on the benzene rings with $TiCl_4$. This interaction causes weakening carbon-carbon bond and this characteristic absorption band (C-C stretching) negatively shifts to 1540 cm^{-1}, indicating coordination of the π bond with the titanium and further confirming the formation of a titanium complex on the surface of the polymer and modification of the phenyl rings of the PS/DVB.

The FT-IR spectra of pyridine adsorbed on PS/$TiCl_4$ Lewis acid and PS samples are shown in Fig. S8. After adsorption of pyridine, the characteristic absorption band at 1450 cm^{-1} is originated C-C stretching vibration in pyridine molecules coordinatively chemisorbed on Lewis sites (Ti), so it was attributed to Lewis acid sites. The other signals for pyridine molecules coordinatively chemisorbed on Lewis sites are about 1493 and 1600 cm^{-1} (C-C ring vibration). However, no band at the same wavelength was observed for the PS sample. Therefore, it was proved that the Lewis acids were successfully immobilized on polystyrene.

The UV spectrum of the solution of PS/$TiCl_4$ complex in CS_2 showed a new absorption band at about 262 nm, which is due to the formation of a stable $\pi \rightarrow$ p type coordination complex between the benzene rings in the polystyrene carrier with $TiCl_4$. UV spectra of PS, PS/$TiCl_4$ are shown in Figure 7S. The probable way of complex formation is shown in Scheme S2 (see supplementary data). As a result of the electron donation from PS moiety to $TiCl_4$, the Lewis acid is stabilized due to the decreased mobility of the benzene rings hindered by the long polystyrene chain. These significant changes revealed that $TiCl_4$ is coordinated with benzene rings through the π bond. The white polystyrene beads becomes pale yellow after the heterogenation with $TiCl_4$ which gives physical evidence of complex formation taking place between $TiCl_4$ and polystyrene beads.

The pH monitoring was used to investigate the acidity changes occurred in a acetone-water solution after adding the PS-$TiCl_4$ complex beads. The pH of PS-supported $TiCl_4$ complex catalyst dispersed in a solution of acetone-water (60%) is shown in Fig. S3 (see supplementary data). It was observed from Fig. S3 that the acidity of solution containing catalyst gradually increased with time. This is due to the liberation of HCl into the acetone-water solution after reaction of $TiCl_4$ incorporated in PS with water. This reveals that there must be a Lewis acid ($TiCl_4$) in the complex. The same experiment was also performed with the naked polymer which shows pH= 6.2 (Fig. S3).

Fig. S4 shows the XRD diffraction pattern of the PS carrier and the synthesized PS/$TiCl_4$ catalyst (see supplementary data). The virgin PS exhibited a broad diffraction peak at (2θ) ranging from 15^o-30^o suggesting the amorphous structure of the polymeric scaffold (see supplementary information). But in case of PS/$TiCl_4$ after incorporation of $TiCl_4$ into the polymer matrix, the intensity of characteristic reflection peak at $2\theta=15^o$-30^o has been considerably diminished without altering the peak position. The reason for the decrease in peak intensity is probably due to the accommodation of $TiCl_4$ molecules onto the PS matrix which combine the polymer chain and it forms complexes with polystyrene. This phenomenon confirms the presence of $TiCl_4$ in the polystyrene matrix.

The incorporating of $TiCl_4$ in PS carrier was also confirmed by using TGA technique. Fig. S5 presents the thermal behavior of the PS and the as-synthesized PS-supported catalyst (see supplementary data). The PS bead showed single step degradation. The initial decomposition temperature of the PS was occurred at about 334 ^oC. The major degradation of the polymer chain occurs in the range of 380-440 ^{o}C (midpoint 422.38 ^{o}C) and the loss is related to breaking the main chain and side group of PS. But in case of $TiCl_4$ incorporated PS catalyst, the weight loss starts at about 50 ^{o}C. This weight loss could be assigned to the release of residual solvent and adsorbed water. Except the slightly initial weight loss, the synthesized PS/$TiCl_4$ showed one step degradation. The major degradation of the polymer chain occurs in the range of 310-450 ^{o}C (50 % weight loss at about 417 ^{o}C and (80% weight loss at about 450 ^{o}C). The degradation temperature (2nd) slightly decreases with the incorporation of $TiCl_4$ into the polymer matrix. The lower second degradation temperture of catalyst relative to that of the pristine polystyrene is mainly due to loss of crystallinity of PS by incorporation of $TiCl_4$ and to an outlet of $TiCl_4$ from the polystyrene matrix. The TGA data reveals that PS/$TiCl_4$ catalyst is thermally stable up to 210-270 ^{o}C (depending on percent of $TiCl_4$ loading), and so it may be inferred that this synthesized catalyst is sufficiently thermally stable to be applied for a variety of chemical transformations which is carried out in that temperature range including the Knoevenagel condensation.

The DSC analysis provide analogous information (Fig. 1). The maximum decomposition temperature (50 wt.% weight loss) for the copolymer bead prepared is about 417 ^{o}C. No exothermic peak in the range 200-250 ^{o}C was observed. For this peak, polymer cross-linking is responsible. Absence of such peaks in the case of copolymer beads prepared indicates that all double bonds of monomers were consumed during copolymerization.

<Figure 1>

To obtain a visual image of the polymer support and the distribution of the titanium species on the polymer support, the SEM micrographs of the beads and the synthesized PS/$TiCl_4$ were prepared. A clear change in morphology was observed after incorporating $TiCl_4$ onto the polymer support. Fig. S6 shows the SEM images of the PS carrier and the sample after immobilization (see supplementary data). From the Figure S6, it can be seen that the PS carrier exhibits randomly regular shape particles and almost non uniform in their sizes with an average diameter of 100 μm. In the case of catalyst after incorporation of $TiCl_4$ on the polymer matrix, randomly irregular aggreagated particles were observed. Moreover, it was observed that the particle size becomes considerably larger than the pristine one and the surface becomes slender smooth. The observed increase in particle diameter of the catalyst particle could be a further evidence of an effective incorporating of $TiCl_4$ with the polymer. The above result is a clear indication of the chemical immobilization of the active catalyst on the support of PS.

The loading capacity of the polymeric catalyst based on its chloride content obtained by gravimetric method and checked by atomic absorption technique was 0.673 mmol $TiCl_4$/g of complex catalyst beads [31]. The data obtained by these two techniques showed, within experimental error, that the catalyzing species are in the form of $TiCl_4$ supported on the polymeric support.

To verify the incorporation of $TiCl_4$ Lewis acid onto polystyrene, BET surface area and pore volume of PS and PS/$TiCl_4$ were measured. In Table S1, porous structure parameters of the studied PS and PS/$TiCl_4$, and catalyst loading of PS/$TiCl_4$ are presented. As surface area of PS carrier bead is almost totally contributed by its open pore system, the catalytic functional group prepared via this scheme should have been evenly confined in the pores. After immobilization, the BET surface area of PS decreased from 42 to 12.24 m^2/g and pore volume decreased from 0.14 to 0.035 ml/g due to the loading of $TiCl_4$ in the pores. The reduction of both surface area and pore volume of the catalyst compared to the original PS support confirms the presence of Lewis acid moieties within the pores of the support. The structure of the parent material (polymer chain) was unaffected after this step; however, a decrease in the PS surface area, as well as some blockage of pores and a slight decrease in the mean pore size are observed, as expected (Table S1, supplementary data).

3.2. Catalytic activity of the PS/$TiCl_4$ catalyst on Knoevenagel condensation

It is well known that titanium chloride as a strong Lewis acid shows unique reactivity in various organic and polymerization reactions [32]. However, it is found to be highly toxic, corrosive, and moisture sensitive, and so its usage, storage, and separation from the reaction mixture were invariably difficult; the strictly anhydrous conditions and stoichiometric amounts or more are required in order to achieve good yields. Moreover, several molar equivalents of triethylamine to titanium tetrachloride are also needed to improve the reaction yields. Therefore, we thought to develop reagent by incorporation of $TiCl_4$ on the organic PS support. The resulting polymer protected reagent, a stable tightly bound complex between anhydrous $TiCl_4$ and PS-DVB copolymer beads was used for the condensation of aromatic aldehydes with 1,3-dicarbonyl compound.

To check the potency of polystyrene-supported $TiCl_4$ catalyst as a heterogeneous catalyst, it was used in the Knoevenagel condensation (which is a versatile and most suited method for generation of C-C bond in organic synthesis). To test the reactivity of β-diketones, a condensation between benzaldehyde and 1,3-diketone (acetylacetone) was initially chosen as a model reaction and was investigated under various experimental conditions to optimize the reaction efficiency. The reaction conditions were optimized, and the results are presented in Table 1. It was found that the best system for this reaction was solvent-free in combination with the reaction temperature 60 ^{o}C, which yielded a 100% conversion of benzaldehyde within 2 h using 10 mol% of the PS-$TiCl_4$ complex (with respect to the $TiCl_4$ content in PS/$TiCl_4$) (entry1) relative to benzaldehyde. We checked the conversion by ^{1}H NMR at maximum after 2 h and the reactions were monitored by TLC, and the consumption of aldehyde was measured. Also, we examined the effect of catalyst loading and reaction temperature on the model reaction. The loading of the catalyst was reduced down to 5 mol% by prolonging the reaction time in order to get full conversion. Increasing the amount of catalyst loading from 74 mg to 222 mg significantly increased the yield and decreased the reaction time (Table 1, entries 9,15,17). However, it was found that the reaction was not completed without an efficient and required amount of the catalyst, 5 mol% PS/$TiCl_4$ gave a conversion of 80% after 6 h while 10 mol% PS/$TiCl_4$ was sufficient to get full conversion after 2 h (Table 1, entries 15,17). A further increase in the amount of catalyst did not exhibit any advantage on the product yield. Therefore, using 120 mg (0.1 mmol) of PS/$TiCl_4$ under sovent-free conditions was deemed ideal for reaction (Table 1, entry 15). Whereas decreasing the amount of catalyst leads to a decrease in the product yield. The optimal conditions for the Knoevenagel condensation with a broad range of aromatic aldehydes and yield (conversion) of the adduct products are listed in the Table 2.

In order to confirm that the catalytic activity arises from the Lewis acid $TiCl_4$ moiety of the polystyrene-supported catalyst, a control experiment or the matrix influence for the condensation reaction was performed by taking benzaldehyde and acetylacetone in the absence of any catalyst and solvent or using PS carrier alone at room temperature; no reactions occurs, and the starting components remain unreacted (Table 1, entries 1,4). In order to improve the experimental results, the reaction was also performed under solvent-free conditions without any catalyst or in the presence of PS carrier alone at 60 ^{o}C and 70 ^{o}C, no conversions were observed, respectively (Table 1, entries 2,3). It is found that the initial reaction (convert to its enolic form) starts merely in the presence of an efficient amount of the catalyst and that on a cross-linked PS surface, acetylacetone is unreactive in the condensation reaction. Also, PS/$TiCl_4$ was found to be a more effective catalyst than PS/$AlCl_3$ for Knoevenagel reaction under identical conditions (Table 1, entry 18).

The reaction temperature played a crucial role in determining the activity of the heterogeneous polystyrene-supported $TiCl_4$ for the synthesis of the Knoevenagel adducts.

The effect of reaction temperature on the catalyst was investigated by performing the condensation of benzaldehyde and acetylacetone under solvent-free conditions at different temperatures. When the reaction was performed at room temperature (25 ^{o}C) under solvent-free conditions, only a conversion 35% was achieved. As the temperature of the reaction was increased to 40 ^{o}C, the reaction conversion increased to 53%. As the product yield increases with increase of temperature, we further performed the reaction at three other higher temperatures like 50, 60 and 70 ^{o}C. From the data in Table 1 , it is clear that the temperature of 60 ^{o}C is the optimal temperature for completion of this reaction (Table 1, entry 15) and at lower temperatures, even if the time was prolonged to 6 h, only low yields were observed (Table 1, entries 13-15). Beyond 60 ^{o}C, no remarkable improvement in the product yield was observed. The reason why a higher temperature was necessary seems to due to the acidity of PS/$TiCl_4$ was weaker than that of anhydrous $TiCl_4$. In addition, this may be explained to be a result of the difficulty associated with the diffusion of the reactants or molecular mass transfer process due to the unfavorable polystyrene micropores and channels. Therefore, the generation of active sites requires temperature pretreatment. In order to compare the catalytic activity of the homogeneous phase and heterogeneous phase at the same reaction temperature and to clarify the role of the PS carrier, we have performed the catalytic reaction of benzaldehyde and acetylacetone in the presence of $TiCl_4$ as the homogeneous phase at 60^{o}C under solvent-free conditions. This data clearly suggests that the microporous polystyrene as support plays a crucial role in this condensation reaction. On complexation of PS support with $TiCl_4$, it is stabilized due to the decreased mobility of the benzene rings hindered by the long polystyrene chain and no need the several equivalents of organic base such as, triethylamine to stabilize $TiCl_4$ and the improve of reaction yields [33,34]. These functionalities, as well as the surface area are absent in the homogeneous catalyst of $TiCl_4$. Thus, the yield of the condensation product over our reusable and heterogeneous polystyrene-supported $TiCl_4$ is much higher than the homogeneous $TiCl_4$ form and also could be avoid tedious extra wok up after completion of the reaction and reduce the amount of acidic waste water generated.

To survey the generality of the catalytic protocol using the heterogeneous catalyst, we investigated the reaction using a variety of aldehydes, including aromatic/heterocyclic/α,β-unsaturated aldehydes with acetylacetone under the optimized condition (Scheme 1). The results are shown in Table 2 (entries 1-9). The electron-neutral, electron-rich and electron-poor aromatic aldehydes reacted with acetylacetone very well. The catalytic performance was excellent for the substrate with electron-withdrawing groups (Table 2, entries 3,4,5,6), which exhibited higher reactivity. Nevertheless the efficiencies were only slightly lower for the substrates with electron-donating groups, because of the decreased activity (Table 2, entries 2,3,7). The reaction conditions were mild enough not to induce any damage to moieties, like the methoxy group (Table 2, entry 3), which often undergo cleavage in the presence of strong acids or certain Lewis acids. Moreover, the protocol could also work equally well with the acid and base sensitive heterocyclic aldehydes, and excellent yields were obtained (Table 2, entry 8). We tried to extend the procedure to α,β-unsaturated aldehydes and the satisfactory results were obtained. In fact the reaction of acetylacetone with cinnamaldehyde gave only the desired condensation product in high yield, which retained the double bond geometry, and no 1,4-addition product was detected (Table 2, entry 9).

Based on these results, we decided to investigate the behavior and catalytic activity of the heterogeneous catalyst PS/$TiCl_4$ in the Knoevenagel condensation reactions between β-ketoesters (ethyl/methyl acetoacetate) and various aldehydes, including aromatic /heterocyclic/α,β-unsaturated aldehydes using 10 mol% of catalyst at 60 ^oC in a solvent-free conditions. The results are summarized in (Table 2, entries 10-21). Compared to the Knoevenagel reactions of acetylacetone with aromatic/heteroaromatic aldehydes, the reactions of ethyl/methyl acetoacetate with the same aldehydes needed more time because of the decreased activity. On the other hand, asymmetric systems like (Table 2, entries 10-21) took longer times to give the corresponding Knoevenagel adducts in good yields even if two isomeric products are formed, the *Z*-isomer usually being predominant. The adduct products of ethyl/methyl acetoacetate were a mixture of *Z*- and *E*-geometical isomeric alkenes and the assignment of stereochemistry of different configurations was made on the basis of the chemical shifts of CH=C, which migrated to lower field for the *E*-isomers as confirmed by ^1H NMR. For example, the reaction between ethyl acetoacetate and *p*NO_2-benzaldehyde gave adduct **3cj** containing a mixture of *E*/*Z* geometrical isomers in the ratio 5:1. However, *o*NO_2-benzaldehyde and *o*Cl-benzaldehyde gave adduct products **3cf** , **3ce** containing *E*/*Z* isomers in the ratio 5:5. Compound which shows lower δ value for $COCH_3$ protons were assigned as *E*-isomer, where COOEt is trans to the aromatic ring and the other compound as *Z*-isomer. The lower δ value for $COCH_3$ protons could be attributed to the effective shielding by benzene ring which is positioned cis to $COCH_3$ group. Moreover, the performance of the PS-$TiCl_4$ complex catalyst was examined in the Knoevenagel reactions of dimethyl malonate with aromatic aldehydes under optimized conditions and the Knoevenagel adducts were obtained in good yields (Table 2, entries 24-26).

<Table 1>

<Table 2>

The effect of crosslinking on the reactivity of the polymeric catalyst in the Knoevenagel reaction was studied. It was found that as the proportion of the crosslinking agent increases the penetration of the solvent and reactants to the active sites of the polymer becomes more difficult because of the highly crosslinked network structure. With higher extents of crosslinking the polymer matrix becomes more rigid and the penetration of the solvent and reactant molecules to the active sites of the catalyst is more difficult. Access to the reactive groups on highly crosslinked networks is considerably diminished as they are flanked by a large frequency of crosslinks leading to a decreased reactivity. Highly crosslinked resins were mechanically stable and rigid, but lacked reactivity.

3.3. Heterogeneity test and catalyst reuse

Next, in order to establish the recyclability and reusability of the catalyst (PS/$TiCl_4$), the condensation reaction under similar conditions, between benzaldehyde and acetylacetone, was taken as the representative case. After the reaction was over, the PS/$TiCl_4$ was separated from the reaction mixture, washed with ethyl acetate thoroughly. Then the recovered catalyst was dried and used for a further five additional reaction cycles. It was used for 5 cycles and almost retained its catalytic activity in these repeating cycles, but consecutive cycles required more time to complete. In all cases, the catalyst exhibited consistent catalytic activity, establishing the recycling and reusability of the catalyst without any significant loss of catalytic activity. Only a very small drop in the reaction conversion in each catalytic cycle is observed and 93% conversion was achieved for 3 h at the fifth cycle (Table 3, Run 5). The result of recycling is shown in Table 3. The supported catalyst is stable under the reaction conditions, but stirring provokes some etching in the beads of the immobilized catalyst leading to a decrease in the effective catalyst loading as the series of experiments progresses. Moreover, a small drop in the 4rd and 5rd cycles may be explained by a considerable decrease in the catalyst mass during the recycling procedure. Nonetheless, the typical IR bands of the immobilised $TiCl_4$ and crosslinked polystyrene backbone after the catalytic cycles remained unchanged, indicating the stability of the catalytic active species and support itself under the catalysis experimental conditions. Hence, the loss of catalytic activity with the reuse of the catalyst may be due to slight leaching of active species, promoted by some degradation of the bond between the support and Lewis acid.

<Table 3>

In order to ascertain whether the catalyst was behaving in a truly heterogeneous manner, or whether it is merely a reservoir for free form of $TiCl_4$ released into the acetylacetone, hot filtration test was performed. In a typical experiment, crosslinked polystyrene-$TiCl_4$ complex and acetylacetone were taken in a round-bottomed flask and stirred at 60 ^oC for 30 min. At this stage, the catalyst was filtered off and the experiment was continued, after adding benzaldehyde to the filtrate, for another 5 h at the same conditions, no reaction took place (Table 1, entry 20), as is evident from the GC analysis. It is confirmed the heterogeneous character of the catalytically active species and that release of $TiCl_4$ is negligible. We also carried out a heterogeneity test for the Knovenagel model reaction, which was done at 60 ^oC in order to check whether the catalyst was truly behaving heterogeneously or not. The catalyst was separated from the reaction mixture by filtration after 30 min of the reaction, and the "catalyst-free" filtrate obtained was continuously stirred under the same reaction conditions for another 1h. Analysis of the filtrate showed no further progress of reaction even after 1 h and no increment in the % conversion was noticed. Catalyst was filtered off at the reaction temperature (60 ^oC) in order to avoid readsorption of leached titanium chloride on the catalyst surface on cooling. This again suggest that there is no loss catalyst components during the course of the reaction, which confirmed the heterogeneity of the catalyst.

According to the results above and based on the literature [33,34], the possible mechanistic pathway, which is shown in Scheme 2, was proposed for the clarification of the catalytic role of PS/$TiCl_4$ in the reported method. The reactivity pattern of aromatic aldehyde indicates that the Lewis acid catalyst, PS/$TiCl_4$ forms a complex with the carbonyl group of 1,3-dicarbonyl compounds first. The complexation increases the acidity of the α-hydrogen atoms because of the electron-withdrawing effect of the electron-poor titanium (IV). Thus the dicarbonyl can be easily deprotonated and converted into the titanium enolate ion. Second, while the activation of aldehyde by titanium center and the formation of strong Ti-O bond, the reactive titanium species undergoes nucleophilic attack to the carbonyl carbon atom and generates the requested Knoevenagel adduct. Therefore, the formation of a strong Ti-O seems to be involved in the water elimination step. According to this mechanism, titanium species would not only help the formation of the corresponding enolate but could also promote the nuclophilic attack reaction of titanium enolate to the polarized carbonyl group of the aromatic aldehyde.

<Scheme 2>

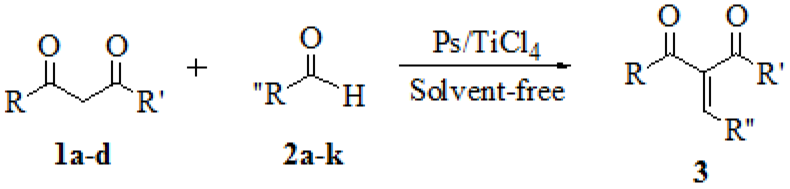
In order to establish the catalytic activity of PS/$TiCl_4$ complex and greenness of this method, we compared our results on the synthesis of Knoevenagel adduct with data from the literature (Table S2, supplementary data). As shown, the most of the former catalytic systems have been performed in the organic solvents at higher reaction times than the PS/$TiCl_4$ catalyst.

4. Conclusion

In summary, we have synthesized the first DVB-crosslinked PS-$TiCl_4$ complex for the use as a heterogeneous Lewis acid catalyst. Cross-linked polystyrene copolymer porous beads with the average particle size in the range of (50-80 mesh) were synthesized via cross-linking suspension copolymerization using guar gum as a new biopolymer suspension stabilizer and functionalized with $TiCl_4$ via complex formation to create surface active acidic sites. PS/$TiCl_4$ was shown to be an efficient and recyclable catalyst for the solvent-free Knoevenagel condensation reaction of less reactive 1,3-diketones with various aldehydes.

Acknowledgement

The authors are thankful to TPC for providing the required chemicals and the Shahid Beheshti University Research Council for partial support of this work.



R= Me, OMe ; R'= Me, OMe, OEt
R"= Ph, *p*MeC_6H_4-, *p*OMeC_6H_4-, *p*ClC_6H_4-, *o*ClC_6H_4-, *o*$NO_2C_6H_4$-, *p*OHC_6H_4-, 2-Furyl, PhCH=CH- (*E*), *p*$NO_2C_6H_4$-, *p*CNC_6H_4-

Scheme 1. Knoevenagel condensations of less reactive methylene compounds (β-diketone and β-ketoesters) and dimethyl malonate with aromatic aldehydes catalyzed by PS/$TiCl_4$

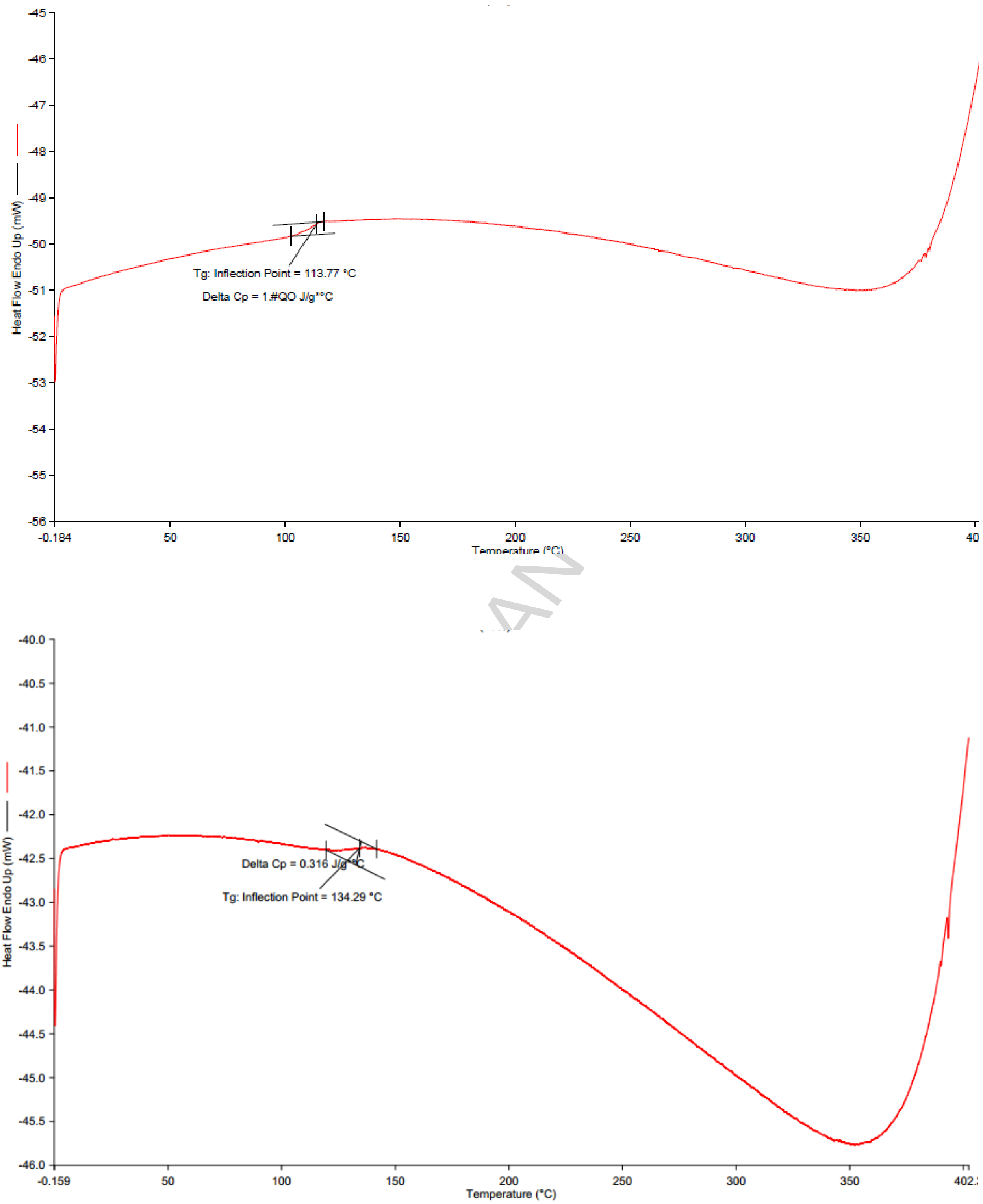
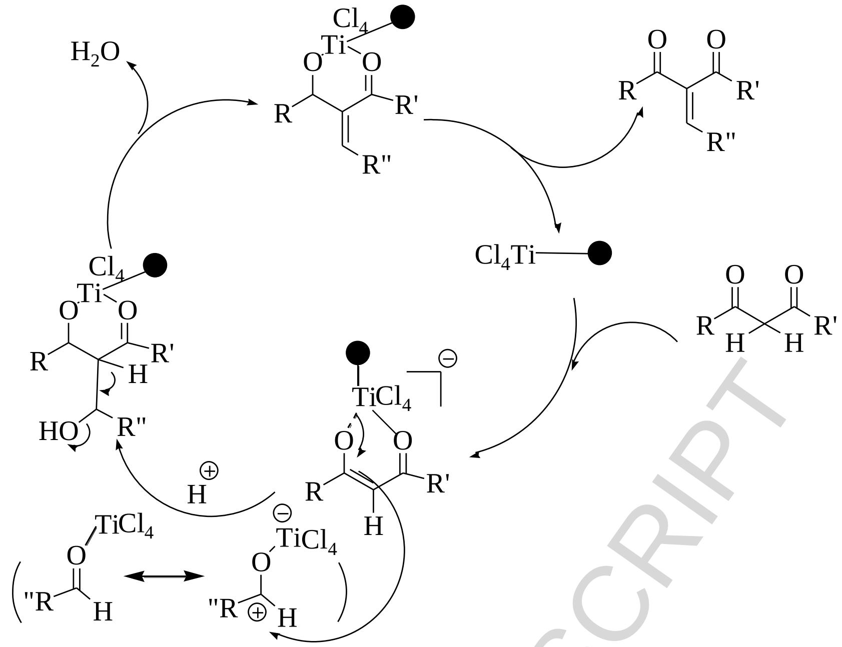


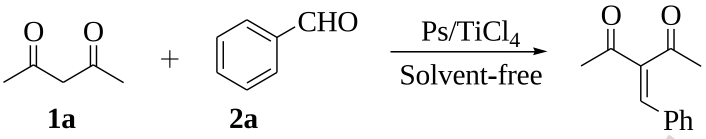
Figure 1. DSC thermograph of the copolymer beads (PS/DVB) at 6 and 10 wt.% DVB (up and down, respectively)



Scheme 2. Proposed mechanism of the Knoevenagel condensation catalyzed by PS/TiCl$_4$

Tables

Table 1
Optimization of reaction conditions for Knoevenagel condensation of benzaldehyde with acetylacetone[a]



1a **2a** **3aa**

Entry	Catalyst	amount	T (^{o}C)	Time (h)	Conversion (%)[b]
[f]1	-	-	rt[g]	10	c
[f]2	-	-	60^{o}C	6	c
[d]3	PSt	-	60^{o}C , 70^{o}C	6	c
[d]4	PSt	-	rt	10	c
5	Toluene/$TiCl_4$		60^{o}C	6h	34
6	PSt/$TiCl_4$	15 mol%	rt	6h	39
7	PSt/$TiCl_4$	10 mol%	rt	6h	30
8	PSt/$TiCl_4$	15 mol%	70	1.4	100
9	PSt/$TiCl_4$	15 mol%	60	1.5	100
10	PSt/$TiCl_4$	15 mol%	50	3	88
11	PSt/$TiCl_4$	15 mol%	40	3	66
12	PSt/$TiCl_4$	10 mol%	rt	6	35
13	PSt/$TiCl_4$	10 mol%	40 ^{o}C	6	53
14	PSt/$TiCl_4$	10 mol%	50 ^{o}C	6	84
15	PSt/$TiCl_4$	10 mol%	60 ^{o}C	2	100
16	PSt/$TiCl_4$	10 mol%	70 ^{o}C	2	100
17	PSt/$TiCl_4$	5 mol%	60 ^{o}C	6	80
18	PSt/$AlCl_3$	10 mol%	60 ^{o}C	3	80
19	$TiCl_4$	10 mol%	60 ^{o}C	2.5	64
[e]20	PSt/$TiCl_4$	10 mol%	60 ^{o}C	30 min	26

[a] *Reaction conditions*: benzaldehyde (1 mmol), β-diketone (acetylacetone) (6 mmol), solvent-free; [b] Referred to the reacted benzaldehyde, conversion determined by GC and ^{1}H NMR. [c] Products were not found. [d] Reaction carried out according to footnote[a], using unfunctionalized cross-linked PSt as a catalyst. [e] The catalyst was filtered after 30 min. [f] Without PSt/$TiCl_4$. [g] r.t. refers here to 25 ^{o}C.

Table 2. Knoevenagel condensations of aromatic aldehydes with β-diketone (acetylacetone)[a] and β-ketoester (ethyl/methyl acetoacetate)

Entry	R	R'	R''	Time (h)	Yield (%)[b,c,d] (*E*/*Z* ratio)	Product
1	Me	Me	Ph	2	98	**3aa**
2	Me	Me	*p*MeC$_6$H$_4$-	2.5	97	**3ab**
3	Me	Me	*p*OMeC$_6$H$_4$-	3	96	**3ac**
4	Me	Me	*p*ClC$_6$H$_4$-	2	98	**3ad**
5	Me	Me	*o*ClC$_6$H$_4$-	2.5	96	**3ae**
6	Me	Me	*o*NO$_2$C$_6$H$_4$-	2	97	**3af**
7	Me	Me	*p*OHC$_6$H$_4$-	3	94	**3ag**
8	Me	Me	2-Furyl	2	98	**3ah**
9	Me	Me	PhCH=CH-(*E*)	3	93	**3ai**
10	Me	OMe	Ph	2.5	97 (44:56)	**3ba**
11	Me	OMe	*p*MeC$_6$H$_4$-	3.2	95 (36:64)	**3bb**
12	Me	OMe	*p*OMeC$_6$H$_4$-	3.5	96 (48:52)	**3bc**
13	Me	OMe	*p*ClMeC$_6$H$_4$-	2.5	96 (49:51)	**3bd**
14	Me	OMe	*o*NO$_2$C$_6$H$_4$-	2.5	95 (0:1)	**3be**
15	Me	OMe	2-Furyl	2.5	97 (46:54)	**3bf**
16	Me	OMe	PhCH=CH-(*E*)	3.5	92	**3bi**
17	Me	OEt	Ph	3.5	93 (25:85)	**3ca**
18	Me	OEt	*p*MeC$_6$H$_4$-	3.5	93 (42:58)	**3cb**
19	Me	OEt	*p*OMeC$_6$H$_4$-	3.5	95 (44:56)	**3cc**
20	Me	OEt	*p*ClC$_6$H$_4$-	2.5	95 (43:57)	**3cd**
21	Me	OEt	*o*NO$_2$C$_6$H$_4$-	2.5	93 (5:5)	**3ce**
22	Me	OEt	*p*NO$_2$C$_6$H$_4$-	2.5	94 (5:1)	**3cj**
23	Me	OEt	2-Furyl	2.5	95 (51:49)	**3ch**
24	OMe	OMe	*p*CNC$_6$H$_4$-	4	94	**3dk**
25	OMe	OMe	*p*NO$_2$C$_6$H$_4$-	4	95	**3dj**
26	OMe	OMe	*p*ClC$_6$H$_4$-	4	94	**3dd**

[a] *Reaction conditions*: aromatic aldehydes (1 mmol), β-diketone (acetylacetone,6 mmol), β-ketoester (ethyl/methyl acetoacetate) and dimethyl malonate, 6 mmol), PSt/TiCl$_4$ (150 mg, 10 mol%, 0.1 mmol TiCl$_4$), Reaction temperature of 60^{o}C, solvent-free. [b] Isolated yield of product or from the weight of the recovered reaction mixture, on the basis of the conversion. [c] The *E*:*Z* geometry was determined by ^{1}H NMR. [d] The IR spectrum of condensation products showed no stretching band of carbonyl group at 1680-1698 cm^{-1}.

Table 3

Recycling potential of the PS/$TiCl_4$ for the Knoevenagel condensation[a]

No of cycles	Fresh	Run 1	Run 2	Run 3	Run 4	Run 5
Yield[b](%)	98	97	96	95	95	93
Time (h)	2	2	2.2	2.4	2.5	3

[a] *Reaction conditions*: benzaldehyde (1 mmol), acetyl acetone (6 mmol), solvent-free, reaction temperature: 60 °C, catalyst (10 mol%).

[b] Isolated yield of pure product.

Table 4

Comparison of the polymeric catalyst PS/$TiCl_4$ with various homogeneous or heterogeneous catalysts in Knoevenagel condensations for the synthesis of **3aa**.

Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield (%)	Ref.
1	L-Tryptophan	DMSO	r.t.	18	60	[8]
2	$Mg(ClO_4)_2$	Neat	r.t.	70	55	[6]
3	$Yb(OPf)_3$	FBS	80	8	80	[9]
4	Organobismuth complex	[Bmim]BF_4	r.t.	6	95	[16]
5	Piperidine AcOH	Benzene	Reflux	18	60	[11]
6	Amino groups immobilized on silica gel (SiO_2-NH_2)	Toluene	25		41	[15]
7	USY zeolite	Benzene	Reflux	6	89	[13]
8	$NbCl_5$	Neat	r.t.	1	85	[7]
9	Magnetic Fe_2O_3 functionalized with ionic liquids	water	80	9	91.1	[36]
10	Silica sulfuric acid	Neat	r.t.	10	66	[18]
11	Zn^{2+} ion-exchanged β zeolite	Neat	140	6	32.2	[14]
12	Perfluoroalkylated pyridine	*n* -Octane	80	8	82	[35]
13	PSt/$AlCl_3$ (10 mol%)	Solvent-free	60	3	80	This work,[37]
14	PSt/$TiCl_4$ (10 mol%)	Solvent-free	60	2	98	This work

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Scheme and Figure captions:

Scheme 1. Knoevenagel condensations of less reactive methylene compounds (β-diketone and β-ketoesters) and dimethyl malonate with aldehydes catalyzed by PS/$TiCl_4$.

Figure 1. DSC thermograph of the copolymer beads (PS/DVB) at 6 and 10 wt.% DVB (up and down, respectively).

Scheme 2. Proposed mechanism of the Knoevenagel condensation catalyzed by PS/$TiCl_4$

Highlights

- Polystyrene copolymer beads were prepared by cross-linking suspension copolymerization.
- Polystyrene-$TiCl_4$ coordination complex was prepared through finctionalization of polystyrene.
- Polystyrene-$TiCl_4$ complex was efficient for the solvent-free Knoevenagel reaction.
- The polymeric catalyst was recovered and reused several times.